therefore, ideally, the response to any treatment should be compared with the long term outcome in that particular abnormality.

## CONCLUSION

Our study, in agreement with previous observations, suggests that long term bosentan treatment is safe, well tolerated, and effective in patients with pulmonary hypertension related to CHD. Careful patient management is recommended in the current monitoring schedule and flowchart for modifying the dosing schedule in cases of increased liver function tests or significant side effects (that is, leg oedema). This is especially relevant in patients with Eisenmenger physiology who usually have multiorgan involvement, and thus may be at greater risk for liver or other organ dysfunction.15 Our safety experience is consistent with the results of the controlled clinical trials8 14 and the wide experience from the bosentan post-marketing surveillance database, in which a large number of patients with PAH-CHD are included.30 A recent larger multicentre, randomised, double blind, placebo controlled study with bosentan in patients with Eisenmenger syndrome confirms these results.

Authors' affiliations

Competing interests: None.

M D'Alto\*, E Romeo, G Santoro, B Sarubbi, P Argiento, M G Russo, R Calabrò, Second University of Naples, A O Monaldi, Naples, Italy C D Vizza\*, R Badagliacca, R Poscia, M Mancone, F Ferrante, F Fedele, Department of Cardiovascular and Respiratory Sciences, University La Sapienza, Rome, Italy

\*M D'Alto and C D Vizza contributed equally to this study.

## REFERENCES

- MacMahon B. McKeown T. Record RG. The incidence and life expectation of children with heart disease. Br Heart J 1953;15:121-9.
- 2 Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. BMJ 1958;46:755-62.
- 3 Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med 2004;351:1655-65.
- 4 Daliento L, Somerville J, Presbitero P, et al. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J* 1998;19:1845–55. **Galie N**, Torbicki A, Barst R, *et al.* Guidelines on diagnosis and treatment of PAH.
- Galle N, Torbicki A, Barst R, et al. Couldelines on diagnosis and freatment of PArt. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J 2004;25:2243–78.
  Hopkins WE, Ochoa LL, Richardson GW, et al. Comparison of the hemodynamics and survival of adults with severe primary pulmonary
- hypertension or Eisenmenger syndrome. J Heart Lung Transplant 1996;**15**:100–5.
- 7 Berman EB, Barst RJ. Eisenmenger's syndrome: current management. Prog Cardiovasc Dis 2002;45:129-38.

- 8 Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896-903.
- Galie N, Seeger W, Naeije R, et al. Comparative analysis of clinical trials and evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 2004:43:81-85
- 10 McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005;25:244–9

  11 Galie N, Manes A, Branzi A. The endothelin system in pulmonary arterial
- hypertension. Cardiovasc Res 2004;61:227-37.
- 12 Tutar HE, Imamoglu A, Atalay S, et al. Plasma endothelin-1 levels in patients with left to-right shunt with or without pulmonary hypertension. Int J Cardiol 1999;**70**:57-62.
- 13 Adatia I, Haworth SG. Circulating endothelin in children with congenital heart disease. Br Heart J 1993;**69**:233–6.
- 14 Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001;358:1119–23.
   Gatzoulis MA, Rogers P, Wei L, et al. Safety and tolerability of bosentan in adults with Eisenmenger physiology. Int J Cardiol 2005;98:147–51.
   Schulze-Neick I, Gilbert N, Ewert R, et al. Adult patients with congenital heart discovered by the content of the content of
- disease and pulmonary hypertension: first open prospective multicenter study of bosentan therapy. Am Heart J 2005;150:716.
- 17 Galiè N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome. A multicenter, double-blind, randomized, placebo-
- controlled study. Circulation 2006;114:48–54.

  18 Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6 min walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985:132:919-23.
- 19 Grossman W. Clinical measurement of vascular resistance and assessment of vasodilator drugs. In: Grossman W, eds. Cardiac catheterization and angiography. Philadelphia, PA: Lea and Febiger, 1991:143–51.
- 20 Christensen DD, McConnell ME, Book WM, et al. Initial experience with Bosentan therapy in patients with the Eisenmenger syndrome. *Am J Cardiol* 2004;**94**:261–3.
- 21 Apostolopoulou SC, Manginas A, Cokkinos DV, et al. Effect of the oral endothelin antagonist bosentan on the clinical, exercise and haemodynamic status of patients with pulmonary arterial hypertension related to congenital heart disease. Heart 2005;91:1447-52.
- 22 Barst RJ, Ivy D, Dingemanse J, et al. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. Clin Pharmacol Ther 2003;**73**:372–82.
- Rosenzweig E, Ivy D, Widlitz A, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. J Am Coll Cardiol 2005;46:697–704.
   Ohlstein EH, Douglas SA. Endothelin-1 modulates vascular smooth muscle
- structure and vasomotion: implications in cardiovascular pathology. Drug Dev Res 1993;29:108-28.
- 25 Morbidelli L, Orlando C, Maggi CA, et al. Proliferation and migration of endothelial cells is promoted by endothelins via activation of ETB receptors. Am J Physiol 1995; 269:686-95.
- 26 Ito H, Hirata Y, Hiroe M, et al. Endothelin-1 induces hypertrophy with enhanced expression of muscle-specific genes in cultured neonatal rat cardiomyocytes. Circ Res 1991;69:209-15
- Takanashi M, Endoh M. Characterization of positive inotropic effect of endothelin on mammalian ventricular myocardium. Am J Physiol 1991:261:611-19
- 28 Otsuka A, Mikami H, Katahira K, et al. Changes in plasma renin activity and aldosterone concentration in response to endothelin injection in dogs. Acta Endocrinol 1989;**121**:361–4
- 29 Chen SJ, Chen YF, Meng QC, et al. Endothelin-receptor antagonist bosentan prevents and reverses hypoxic pulmonary hypertension in rats. J Appl Physiol
- 30 Humbert M, van Lierop C, Kiely DG, et al. Long term safety profile of bosentan in patients with pulmonary arterial hypertension: results from the European surveillance program. Data on file. Allschwil, Switzerland: Actelion Pharmaceuticals, 2004.

## Save your favourite articles and useful searches

Use the "My folders" feature to save and organise articles you want to return to quickly-saving space on your hard drive. You can also save searches, which will save you time. You will only need to register once for this service, which can be used for this journal or all BMJ Journals, including the BMJ.